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# Improvement of GI tolerance of NSAIDs using oral prodrug approach

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## Abstract

*Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used for the management of inflammation, pain and nociception. Gastric intolerance caused by most of the NSAIDs used today restricts their use. Several approaches have been proposed to modify the parent NSAIDs molecule in order to reduce their gastric toxicity. Oral prodrug approach is one of such approaches. This review focuses on the various prodrug approaches used to improve the GI tolerance of NSAIDs.*

**Keywords**: Gastric intolerance, NSAIDs, Prodrugs.

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## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are most widely prescribed drugs for the treatment of various inflammatory disorders including rheumatoid arthritis. However, gastrointestinal, renal and cardiovascular toxicity associated with common NSAIDs limits their usefulness [1-3]. All NSAIDs are believed to inhibit the biosynthesis of prostaglandins by inhibiting the group of enzymes called cyclooxygenases (COX) [3]. In early 1990's, two isoforms of COX were discovered, a constitutive COX-I and inducible COX-II. The COX-I enzyme is located in normal tissues and is cytoprotective, physiologically important for GI and renal functions. On other hand COX-II is pathological, found primarily in inflamed tissues [4-7]. Thus, non-selective COX inhibitors cause inhibition of both the isoforms, producing GI and renal side effects due to inhibition of COX-I. While selective inhibition of COX-II could block the prostaglandin production at the site of inflammation without affecting the beneficial prostaglandin in normal tissues such as stomach and kidneys [8-12]. This led to the development of selective COX-II inhibitors with improved pharmacological profile and reduced gastric toxicity [13]. But the era of COX-II inhibitors soon came to an end due to its cardiovascular side effects on chronic use [11].

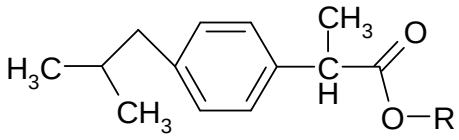
Gastric mucosal injury produced by NSAIDs is generally aggravated by the local irritation caused by acidic group of NSAIDs. Thus temporary masking of this group gives some relief to the patient from GI irritation; hence prodrug approach is the most suitable technique for this purpose.

Present review focuses on various modifications of NSAIDs using prodrug approach, in order to reduce their gastric side effects without affecting their biological potential.

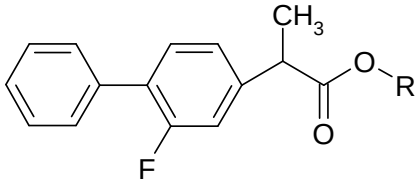
**Different approaches of prodrugs for reduction of GI side effects and ulcerogenicity of NSAIDs**

**(1) Ester and Amide prodrugs of NSAIDs:**

Simple ester prodrugs of NSAIDs like Ibuprofen **(1)**, Flurbiprofen **(2)**, Ketoprofen **(3)** have been synthesized and evaluated. These simple esters were synthesized using simple alcohols like ethanol, isopropyl alcohol etc. This kind of system can easily undergo enzymatic hydrolysis by the action of esterases present abundantly in the small intestine; hence stomach's mucosa is not exposed to the free carboxylic group. Similarly, simple amide prodrugs of Ibuprofen **(4)**, Flurbiprofen **(5)**, Ketoprofen **(6)** have also been reported, wherein simple amines were used to form amide bond with the carboxylic acid. These are more stable in stomach as amidases that bring upon the hydrolysis of amide bond are present only in intestine [14.15].



**(1)**



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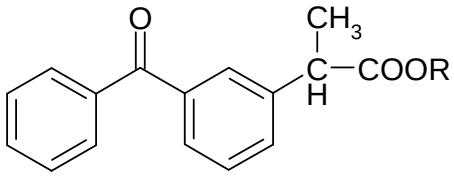

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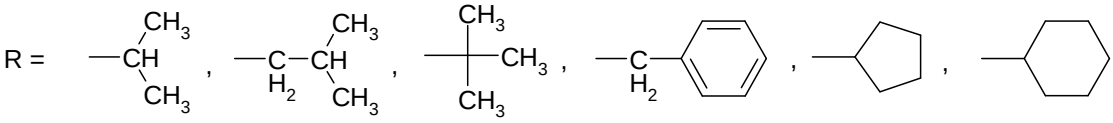

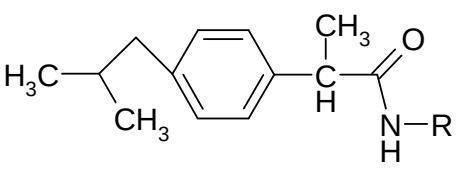

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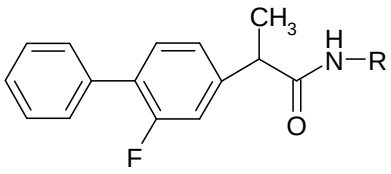

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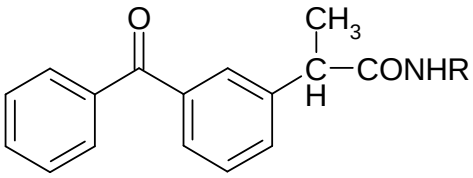
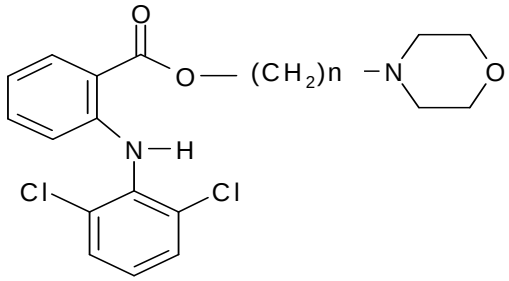


**(6)**

Morpholinoalkyl ester prodrugs of Diclofenac **(7)** have also been synthesized having better log p profile with adequate stability and a high susceptibility to undergo enzymatic hydrolysis in plasma [16].



**(7)**

**(2) Anhydride prodrugs of NSAIDs:**

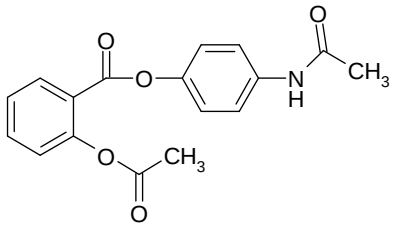
Hydrolysis of the other prodrugs depends on the enzymatic activity, which may vary amongst individuals or even in the same individuals at various times during the day or in various sites where the drug is administered. This fact may result in a large variation of bioavailability. Hence, synthesizing anhydride derivatives of carboxylic acid bearing drugs solved this problem. Unlike the ester bond used in prodrugs, anhydride bond is more susceptible to hydrolysis and decomposition of its carboxylic acid counterparts in a predictable rate and manner and is less sensitive to enzymatic action than the esters and amides [17].

**(3) Mutual prodrugs of NSAIDs:**

Mutual prodrug is a kind of prodrug in which the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug normally comprises of two biologically active agents coupled together so that each acts as a pro-moiety for the other agent and *vice versa*. The carrier may have same pharmacological action as that of parent drug thus giving synergistic effect or it may have some additional pharmacological properties lacking in the parent drug. Thus, giving additional therapeutic advantage or reducing some side effect associated with the parent drug.

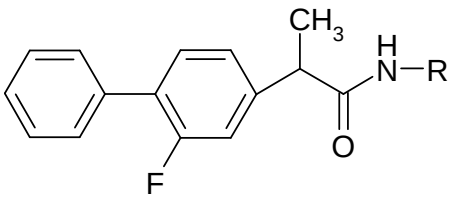
Some of the mutual prodrug approaches are as follows,

**(a)** Benorylate **(8)**: This was the first mutual prodrug of NSAIDs, in which coupling with Paracetamol minimized ulceration caused by aspirin. In this design, hydroxyl group of paracetamol was coupled with carboxylic group of aspirin by an ester bond. This molecule not only improved the gastric tolerance of aspirin but also improved its pharmacological profile due to the synergistic action showed by paracetamol [18,19].



**(8)**

**(b)** Coupling with amino acids: It is well known fact that amino acids have inherent anti-inflammatory and anti arthritic activity. Moreover amino acids can easily be consumed by the body, thus in this model amino acids are coupled with NSAIDs through ester and amide bonds. Hence, this type of system also shows synergistic anti-inflammatory effect along with the reduction in ulceration. These kinds of prodrugs also exhibit enhanced partition coefficient and solubility. Amino acids like L-tryptophan, L-histidine, L-glycine are carriers that have marked activity of their own [20,21]. Such prodrugs of flurbiprofen **(9)** and ketoprofen **(10)** have been cited below.



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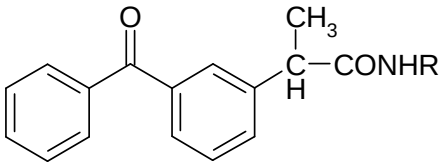

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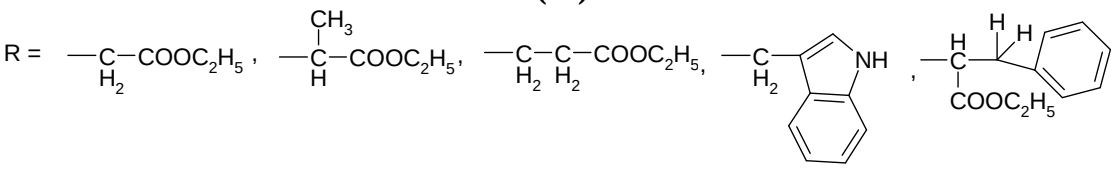
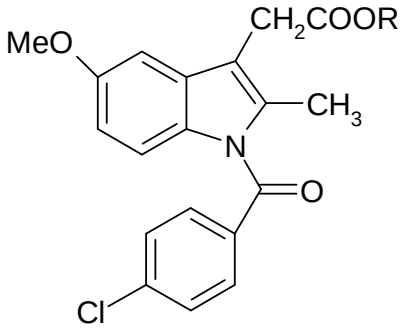


**(c)** Aminoalcohol ester analogues of Indomethacin **(11)**: In this type indomethacin was coupled with aminoalocohols having structural resemblance with aminoethanol ester class of anticholinergics. Thus blocking the acidic functionality of Indomethacin along with the anticholinergic effect. Gastric toxicity is reduced considerably not only because of blockage of acidic group but also due to the cessation of gastric acid secretion caused by local inhibition. Hydrolysis of such entities leads to the formation anticholinergic molecules in intact form. These N,N-disubstituted aminoalcohol esters were specifically designed to possess a terminal tertiary nitrogen atom with an ethylene bridge between this terminal nitrogen and carbonyl group of bulky ester, which are also the structural features of anticholinergics [22].



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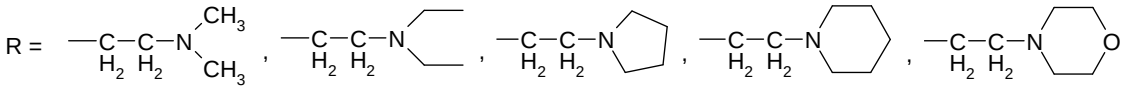
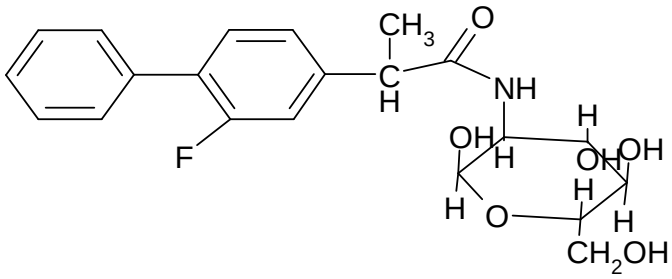


**(d)** Glucosamine conjugate prodrug of NSAIDs: In this type of prodrug, Glucosamine is conjugated with NSAID's like Flurbiprofen **(12)**. The rationale behind the use of glucosamine is to mask COOH group temporarily. Glucosamine is an amino sugar, which is physiologically used by the body to produce natural joint components like critical joint lubricants and shock absorbers. Glucosamine hydrochloride and sulphate are being used as anti arthritic agents as well as a nutritional supplement in conditions like joint ache, stiffness severely restricted movements and serious pains. These prodrugs have additional advantage of producing non-toxic, nutrient by-product, i.e., glucosamine on cleavage, which shows the synergistic effect. Glucosamine is also used in wound healing and gastric disorders [23].

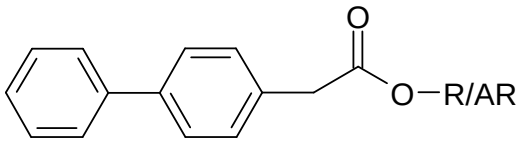
**(e)**



**(12)**

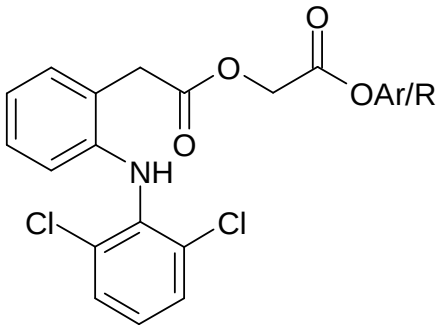
**(f)** Mutual prodrugs of NSAIDs and natural antioxidants: Recent studies have revealed that local generation of various Reactive Oxygen Species (ROS) may be playing a significant role in the formation of gastric mucosal lesions associated with NSAIDs therapy. Based on this fact it has been suggested that co-administration of antioxidants and NSAIDs in formulated dosage forms may possibly decrease the risk of NSAIDs induced GI toxicity and ulcerogenic side effects. Moreover, these phytoconstituents are of natural origin hence they are biodegradable [24,25]. Number of approaches has been put forward in this direction; two of them are listed below.

1. Mutual prodrugs of 4-biphenyl acetic acid and phytophenolics **(13)**: In this approach 4-bipheny acetic acid was coupled with phenolic antioxidants like thymol, guaiacol,eugenol as well as alcoholic compound menthol by an ester bond [24].




**(13)**

2. Diclofenac- antioxidants prodrugs **(14)**: Here, Diclofenac was conjugated with natural antioxidants like vanillin, sesamol, umbelliferone using glycolic acid spacer (-$OCH_2COO$-) [25].

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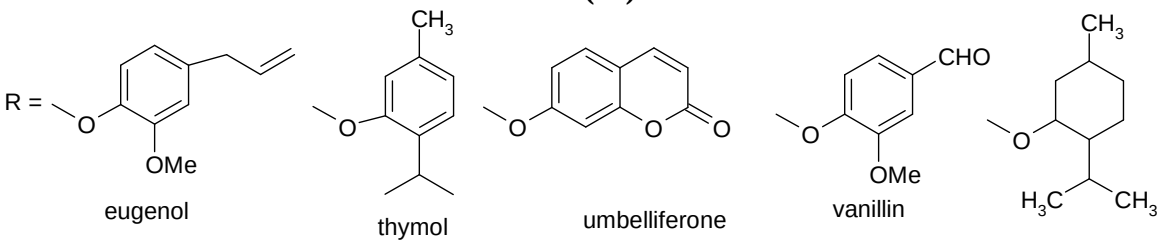
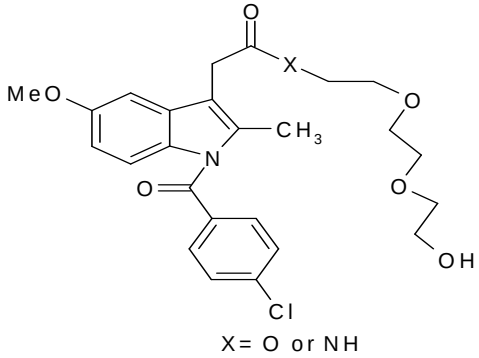


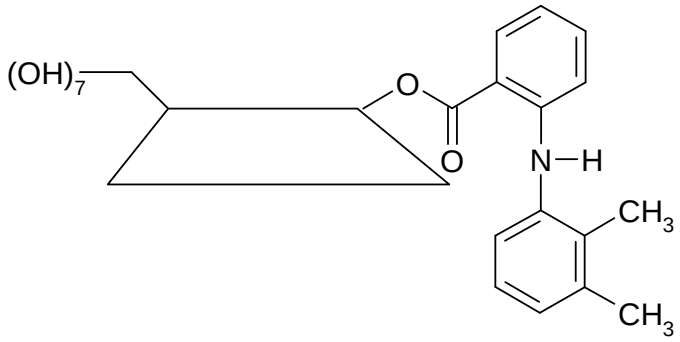

(f) Polyethylene glycol (PEG) and triethyleneglycol(TEG) prodrugs of Indomethacin **(15)**: In this approach Indomethacin was conjugated with PEG or TEG by an ester or amide linkage. This sort of entity minimizes gastric irritation and also increases absorption due to improved solubility in




**(15)**

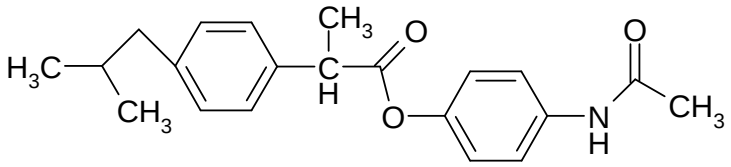
aqueous solutions. In addition, PEG and TEG are inert and do not impart any undesired effect on the body [26].

**(g)** Cylodextrin conjugate prodrug of mefenamic acid **(16)**: In this case, Mefenamic acid was conjugated with ß-cyclodextrin via ester bond. Mefenamic acid belongs to the family of *N*-aryl anthranilic acid. It is widely used in rheumatic disorders such as ankylosing spondilytis and rheumatoid arthritis. Its main side effect includes GIT disturbance, peptic ulceration. Cylodextrins are moderately soluble in water, methanol and readily in aprotic solvents. After oral administration, cyclodextrins are not hydrolysed during their transit time through the stomach, hydrolysis occurs only in colon by colonic micro flora. The oral administration of cyclodextrins does not results in toxicity. Hence, this approach can be used for colon targeting and to avoid the exposure of free drug to the stomach. Cylodextrin conjugate of mefenamic acid retains the pharmacological profile of mefenamic acid. *In-vitro* hydrolysis studies showed that the ester is quite stable in simulated gastric and intestinal fluids, where as it are easily hydrolysed in rat faecal matter representing the colon [27].




**(16)**

**(h)** Mutual prodrugs of ibuprofen with paracetamol **(17)** and salicylamide **(18)** have been reported with better lipophilicity and reduced gastric irritancy [28].

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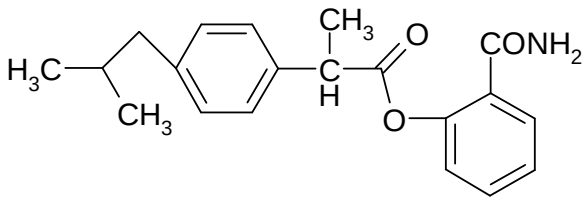
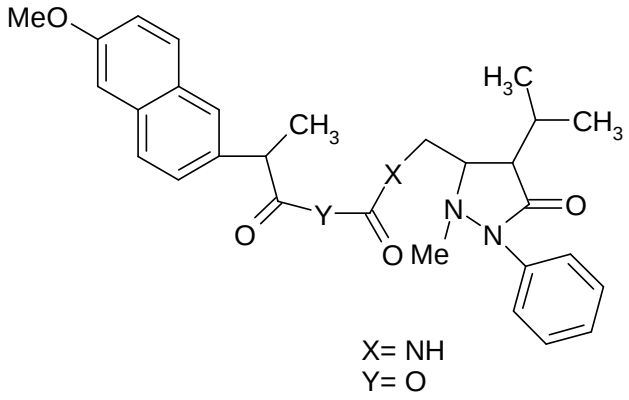



**(18)**

**(i)** Naproxen propyphenazone mutual prodrugs **(19):** These were synthesized with an aim to improve therapeutic index through prevention of GI irritation and bleeding. Esterification of naproxen with different alkyl esters and thio esters led to the prodrugs with retained anti inflammatory activity but exhibited reduced erosive properties and analgesic potency, but

estrification with ethyl piperazine showed that analgesic activity was preserved where as anti-inflammatory activity was generally reduced. Propyphenazone is converted to its active metabolite, 3-hydroxy methyl propyphenazone, which actually gives the analgesic effect [29].

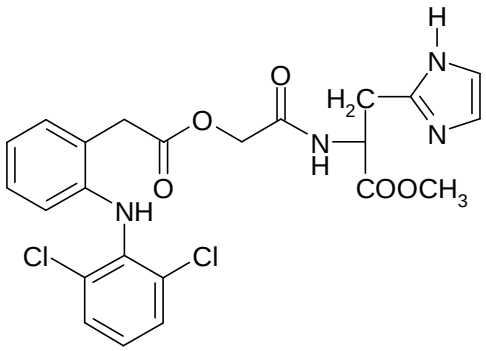



**(19)**

**Newer Approaches**

**1.** Nitric oxide releasing prodrugs: A more recent approach for making a gastric-sparing NSAIDs involves chemical coupling of nitric oxide (NO) releasing moiety with the parent NSAID. Studies have shown that the use of NSAID's with NO-releasing properties has an improved GI safety. Along with prostaglandins, NO plays an important role in cytoprotection in GI homeostasis and defense by helping to maintain mucosal blood flow. Thus NO may counteract the harmful effects of COX. Synthesis of NO-releasing organic nitrate esters of several NSAIDs like aspirin, diclofenac, naproxen, ketoprofen, flurbiprofen has been reported with comparable anti-inflammatory activity and reduced GI toxicity as compared to their parent molecules. Unlike COX-2 inhibitors and standard NSAIDs, NO-releasing NSAIDs mutual prodrugs have shown existing ulcer-healing properties in rats. NO-releasing diclofenac ester prodrugs with tertiary nitrosothiols as NO-donors, NO-releasing furoxan esters of ibuprofen and NO-releasing furazan esters of naproxen have been reported with reduced gastric toxicity [30].

**2.** Aceclofenac colon specific mutual amide prodrug: This is a relatively a new approach, in which carboxylic group of aceclofenac was masked with methyl esters of amino acids through an amide linkage. The amino acids like histidine, alanine, glycine, tyrosine were chosen as they posses inherent anti-inflammatory, cytoprotective and immunomodulatory activity which synergies the action of prodrug (structure of aceclofenac and histidine prodrug **(20)** is shown below). Marked hydrolysis of prodrug was observed in rat fecal matter containing colonic enzymes (amidases). Reduction in ulcer index and increase in anti-inflammatory activity was observed for the prodrugs and proved to be better in action in colon as compared to parent drugs [31].



**(20)**

## CONCLUSION

Thus, oral prodrug approach is an excellent approach, which not only increases the GI tolerability of NSAIDs but also improves bioavailability. In some instances it also increases efficacy of the parent drug due to its synergistic action. On other hand, this approach also faces few limitations like the prodrugs cannot be subjected to *in-vitro* biochemical tests such as enzyme inhibition as it needs bioactivation. Sometimes, prodrug may undergo *in-vivo* hydrolysis to form toxic metabolites, which are not usually produced by parent drug. Hence during toxicity studies it has to be considered as a new chemical entity.

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